REDACTED DOCUMENTS RELATING TO DOCKET 7289

EXHIBIT A – Previously filed redacted in DKT 8118

EXHIBIT E – No redactions

EXHIBIT F – No redactions

EXHIBIT I – No redactions

EXHIBIT E

Rebuttal Report to Expert Report of Dr. Ronald Thisted

Summary: This report responds to portions of the Report of Dr. Thisted, dated April 13, 2017. I may or may not agree with opinions of Dr. Thisted and other defense experts upon which I have not commented. The main points of my rebuttal are the following:

- Dr. Thisted blurs the important distinction between the risk ratio and the incidence rate ratio. My report is about estimation of the risk ratio and I do not claim to estimate the rate ratio. These quantities have different purposes and are both useful as comparative measures of risk.
- The reporting risk ratio, which is what can be estimated from available data, is informative about the risk ratio, which is the quantity of interest. This is possible through some plausible assumptions on detection, reporting, and implantation of sold devices, in conjunction with consideration of serious adverse events.
- The FDA website suggests that MAUDE data can be used in conjunction with other data sources to provide information on adverse events. I agree with this, and accordingly identified the caveats and limitations of this analysis in my expert report.
- BARD has made repeated use of IMS sales data and their own internal sales data in their own reports and analyses, and so they apparently did not discount this approach, and they must have assumed that any discrepancy between devices sold and devices implanted was the same across devices.

1. Dr. Thisted claims that I cannot calculate risks of adverse events (23). In fact, I state in my report that I *estimate* risks of adverse events, and in particular, risk ratios for adverse events. By definition, an estimate is not the truth, but rather the closest approximation to the truth given the data at hand, and given a set of assumptions. I made it clear in my report that my estimates are based on reported numbers, which are related to surveillance, reporting, and usage of sold devices, and rely on assumptions.

2. Dr. Thisted claims that the reporting risk ratio in my report has no direct relationship to the rate at which those events occur in patients. I noted this in my report and stated that in order to estimate an incidence rate or incidence rate ratio, I would need to know exposure times. Both the risk measure and the incidence rate measure are widely used in clinical studies and have different purposes. The risk measure captures population level risk relative to a period of time, while the incidence rate captures individual level instantaneous risk. The risk is related to the individual as a member of the population; it is the probability of the event within the designated period of time. It is not a hazard rate or instantaneous rate of the event. For example, a very common endpoint in phase II cancer clinical trials is the six month progression free survival probability. This is the proportion of patients with the particular type of cancer who survive without progression for at least six months from some time origin. This is commonly used within these studies because it is easily understood and it is a meaningful benchmark. Dr. Thisted

states (31) that the simple measure of risk and the risk ratio are not used "because they omit a critical consideration." As I've explained above, the risk and risk ratios are alternative measures that are population level measures, rather than an individual measure of risk.

3. Dr. Thisted (73) compares what he labels as my "reporting rate – x_1/n_1" to the "corresponding adverse event rate – $A_1/(N_1 \times E_1)$." Again, I never refer to x_1/n_1 as a reporting rate or as any rate; I refer to it as a risk. And I never claimed that it corresponds to the adverse event rate. Dr. Thisted makes his point again in (76). As noted elsewhere by Dr. Thisted , I am careful throughout my report to acknowledge two very important aspects of estimation in this context: (1) the distinctions between reported adverse events and actual adverse events and between reported numbers of implants (via sales numbers) and actual numbers of implants and (2) the distinction between risk and incidence rate.

4. Dr. Thisted states that I was not cautious in my Summary conclusions to make the distinction between the RRR and the RR (26). In fact, a close reading of my Summary will show that when I made a statement about the RR, I explained how I was using my estimates of the RRR to make that statement about the RR. For example, in my first bullet point I wrote: "The extremely large magnitudes of the reporting risk ratios suggest that even if there was substantially increased reporting of Recovery relative to SNF (or, equivalently, substantially less [should be "more"] underreporting of SNF), the risk ratios for the adverse events could still be considerably larger than 1." In my concluding Summary paragraph I was careful to acknowledge the RRR as an estimate of the RR that depends on several factors: "In conclusion, the best available adverse event data for the filters considered provide compelling evidence in favor of increased risks of the adverse events that I considered. The reporting risk ratios are generally extremely large, which in association with their very small p-values, multiple sensitivity analyses, and consistency over time, products and AE's, suggest highly robust increased risks of adverse events for Recovery relative to SNF, and similarly, in most cases, for G2 and G2X, and with respect to fractures for Recovery, G2, G2x, Eclipse, Meridian, and Denali. While these may partially reflect some differential reporting, it is implausible that they would be entirely explained by this."

5. Dr. Thisted states (60) that I relied on MAUDE data from the FDA and BARD sales data that was provided by BARD. In fact, the adverse event data were also provided by Bard and are likely related to the MAUDE data, but may not be equivalent and may include more adverse events.

6. Dr. Thisted notes that there may be duplicated reports to MAUDE (63); presumably this would be less of a problem for Bard's internal database of events.

7. Dr. Thisted notes that the FDA warns against using MAUDE (68). However, the FDA also states that information in MAUDE can be useful in conjunction with other information. At the FDA website, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Search.cfm, the following, similar, but more nuanced statement, is provided by the FDA:
   - "MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
   - Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
   - MAUDE data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions."

   Importantly, this FDA statement acknowledges that while MDR data should not be used in isolation, it does not advise against the type of analysis that I used in this case. There is nothing in any FDA statement that I have seen that precludes use of adverse event data in conjunction with other information to establish rates or events, to evaluate changes in event rates over time, to compare event rates between devices, and to make device-related decisions.

   The FDA published a guidance document on this topic, "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment," in 2005 (https://www.fda.gov/downloads/RegulartoryInformation/Guidances/UCM126834.pdf). The document clearly states that analyses of the FDA databases can provide insights into adverse events for a given product, and into comparisons between products. The following are selected quotations from the guidance document:

   "Data mining can be used to augment existing signal detection strategies and is especially useful for assessing patterns, time trends, and events associated with drug-drug interactions."

"Although all of these approaches are inherently exploratory or hypothesis generating, they may provide insights into the patterns of adverse events reported for a given product relative to other products in the same class or to all other products."

"Although we recognize these limitations, we recommend that sponsors calculate crude adverse event reporting rates as a valuable step in the investigation and assessment of adverse events. FDA suggests that sponsors calculate reporting rates by using the total number of spontaneously reported cases in the United States in the numerator and estimates of national patient exposure to product in the denominator."

"Comparisons of reporting rates and their temporal trends can be valuable, particularly across similar products or across different product classes prescribed for the same indication. However, such comparisons are subject to substantial limitations in interpretation because of the inherent uncertainties in the numerator and denominator used. As a result, FDA suggests that a comparison of two or more reporting rates be viewed with extreme caution and generally considered exploratory or hypothesis-generating."

8. Dr. Thisted notes (69,70) that sales data are a proxy for numbers of implants. This is true, but even Bard used sales data in this way for some products for its reports. Sales numbers are an approximation for the number of implants. Unless there is a systematic difference in the relationship between the numbers of sales and numbers of implants for one product versus another, overestimation of the numbers of implants would not affect the reporting risk ratios.

9. Dr. Thisted misrepresents my definition of the risk ratio (80) as the incidence rate ratio. Based on my definition of the RRR, the formula that he gives (80) that relates the RRR to the RR is incorrect; it should not include multiplication by E_1/E_2. Instead it should be: $RRR=RR\times(d_1/d_2)\times(r_1/r_2)\times(f_2/f_1)$. As defined by Dr. Thisted, d_1 is the probability of detection of the adverse event for device 1, r_1 is the probability of reporting the adverse event for device 1 given that it is detected, and f_1 is the probability of implanting device 1 given that it is sold. I argued in my report that if the true RR were equal to one, then we would not expect to see the wide variation in the RRR across devices that we see. This is due to the following reasoning:
    - (f_2/f_1) is constant across adverse events since implantation of a sold device occurs prior to adverse events
    - (r_2/r_1) should be nearly constant across serious adverse events, such as those I have considered in my report
    - (d_1/d_2) should be constant across adverse events since d_1 can be represented as $d_2\times(1+\alpha)$, where α is the relative increase in detected events of a retrievable device relative to a permanent device due to the potential

for increased monitoring or simply due to scheduled retrieval. Importantly, α does not depend on adverse event type.

Thus, the ratio of the RRR for adverse event 1 to the RRR for adverse event 1 should be equal to 1 if the true RR's are all equal to 1. In fact, for the data through July, 2010, for the Recovery vs SNF comparison, this is not the case. The ratio of the RRR for migration to caval perforation is 13.3, for migration versus filter fracture is 9.6, and for caval perforation versus filter fracture is 0.72. Dr. Thisted notes that this apparent variation might simply be due to variability in the RR's (84). I therefore formally tested whether these ratios of RRR's are significantly different from 1 or not, and obtained the following p-values: migration vs caval perforation (p=0.016), migration vs filter fracture (p=0.028) and caval perforation vs filter fracture (p=0.46). Thus, using a significance level of 0.05, there remains a statistically significant difference between the RRR for migration and that for caval perforation, and between migration and filter fracture, indicating that there is evidence that the true RR's for migration and for caval perforation and for filter fracture, for Recovery vs SNF, are not all equal to 1. The fact that the comparison between caval perforation and filter fracture is not significant does not mean that the RR's for each are equal to 1; it simply means that we cannot reject the null hypothesis that they are equal to each other. My original analysis includes confidence intervals that indicate that all of these RRR's are greater than 1.

Rebecca Betensky

Digitally signed by Rebecca Betensky
DN: cn=Rebecca Betensky, o, ou, email=betensky@hsph.harvard.edu, c=US
Date: 2017.05.12 15:16:13 -04'00'

Rebecca A. Betensky, Ph.D.

May 12, 2017
Date

EXHIBIT F

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF ARIZONA

IN RE: Bard IVC Filters Products Liability Litigation,	No. 2:15-MD-02641-DGC

EXPERT REPORT OF RONALD A. THISTED, Ph.D.

I. Background and Qualifications

1. I am an expert in the fields of statistics, biostatistics, mathematics, and epidemiology. In particular, I have training, experience, and expertise in the design, analysis, and review of clinical investigations in a range of clinical areas. I am an expert in statistical methods used in the fields of epidemiology, medicine, biology, and pharmaceutical sciences.
2. I am currently a Professor in the Department of Public Health Sciences, the Department of Statistics, the Department of Anesthesia & Critical Care, the Undergraduate College, and the Committee on Clinical Pharmacology and Pharmacogenomics at the University of Chicago. In this capacity I have taught statistical methods, statistical computation, epidemiology and research design to medical students, graduate students, undergraduate students, medical residents, and fellows.
3. For 14 years, from January 1999 through December 2012, in addition to the roles above, I served as the Chairman of the Department of Health Studies (Public Health Sciences since September, 2014) at the University of Chicago. This Department comprises the fields of biostatistics, epidemiology, and health services research.
4. I currently serve as Vice Provost for Academic Affairs at the University of Chicago, a position I have held since October, 2014.
5. From 2000 until I joined the Provost's Office in 2014, I was the Scientific Director of the Biostatistics Core Facility at the University of Chicago Comprehensive Cancer Center as well as the Biostatistics Consulting Laboratory. My responsibilities included scientific oversight and management of several professional Ph.D. and Master's level statisticians who collaborate with principal investigators studying all aspects of

diagnosis, treatment, and causes of cancer. During my tenure, the Biostatistics Laboratory typically had over 50 funded collaborations in any given year.

6. I obtained a Ph.D. in statistics from Stanford University in 1977, an M.S. in statistics from Stanford University in 1973, and a B.A. in mathematics and philosophy from Pomona College in 1972. I have been a member of the faculty of the University of Chicago Department of Statistics since 1976, and a member of the faculty of the University of Chicago Pritzker School of Medicine since 1989.

7. I was elected a Fellow of the American Association for the Advancement of Science in 1992 and a Fellow of the American Statistical Association in 1988. I am also a member of several other professional societies, including the American Public Health Association, the Institute of Mathematical Statistics, the Royal Statistical Society, the International Biometric Society, and the Association for Computing Machinery. I have served on the editorial boards of several professional journals in the field of statistics, including the Journal of the American Statistical Association. I served as an editor of the Current Index to Statistics, an index to the world-wide statistical literature. I have also served on several University of Chicago committees, including the Research Advisory Committee of the Biological Sciences Division, and the Institutional Review Board.

8. Since the late 1970s, I have consulted for the pharmaceutical and medical device industries on the design of clinical trials and statistical analysis of clinical trials and other clinical and preclinical studies. This work has included consulting regarding the design of Phase I, Phase II, and Phase III clinical trials, designing and implementing data collection methods, supervising data coordinating centers, planning and overseeing statistical analysis of results, overseeing collection and analysis of adverse experience

data, preparing reports for use by the FDA, and meeting with the FDA as part of the drug development process.

9. In the course of my consulting and academic work, I have participated in multiple studies evaluating adverse events and their possible association with specific medical interventions.

10. During the course of my career, I have published more than 110 original articles in peer-reviewed scientific publications, including *The New England Journal of Medicine, The Lancet, Circulation, Journal of the American Medical Association*, and *The Journal of the American Statistical Association*. I have written a book in the field of statistical computation, Elements of Statistical Computing. I have also written over 35 book chapters, comments, reviews and other publications.

11. My curriculum vitae, which describes in greater detail my professional experience and qualifications and which includes a list of publications I have authored in the last ten years, is attached as Exhibit 1.

12. In the last four years, I have provided deposition and/or trial testimony as an expert witness in the following cases:

    a. Warner Chilcott Company, LLC, v Mylan Inc., Mylan Pharmaceuticals Inc., and Famy Care Ltd., US District Court, District of New Jersey, Civil Action No. 3:11-cv-03262-JAP-TJB,

    b. Warner Chilcott Company LLC v Lupin Ltd and Lupin Pharmaceuticals, Inc, U. S. District Court, District of New Jersey, Civil Action No. 11-cv-05048-JAP-TJB and Warner Chilcott Company LLC v Watson

Laboratories, Inc., U. S. District Court, District of New Jersey, Civil Action No. 12-cv-02928-JAP-TJB,

c. Boston Scientific Corporation, Cardiac Pacemakers, Inc., Guidant LLC, and Guidant Sales LLC v Mirowski Family Ventures, LLC, US Dist Court, Southern District of Indiana, Indianapolis Division, Civil Action No. 1:11-cv-0736-WTL (DKL),

d. Mirowski Family Ventures, LLC v. Boston Scientific Corp., Civ No. 373798-V, Montgomery County (MD) Circuit Court,

e. Sucampo AG, Sucampo Pharmaceuticals, Inc., R-Tech Ueno, Ltd., Takeda Pharmaceutical Company Limited, Takeda Pharmaceuticals USA, Inc. and Takeda Pharmceuticals America, Inc. v. Anchen Pharmaceuticals, Inc., Par Pharmaceutical, Inc., and Par Pharmaceutical Companies, Inc., Civ. Action No. 13-202 (GMS) (District of Delaware),

f. Allergan Inc v. Apotex Inc., Federal Court of Canada, Court File T-852-14;

g. Forest Laboratories, Inc., Forest Laboratories Holdings, Ltd, & Royalty Pharma Collection Trust v. Apotex Corp. and Apotex Inc., et al., C.A. No. 13-1602 (SLR) (District of Delaware),

h. Dr. Qingshen Zhu and Dr. Julio Spinelli, acting jointly as the Stockholder Representative Committee for Action Medical, Inc., v. Boston Scientific Corporation and Cardiac Pacemakers, Inc., Civil Action No. 14-542-SLR (District of Delaware),

i. Sanofi et al v. Glenmark Generics Inc. USA, et al., Civil Action No. 14-264-RGA (Dist of Delaware), and

j. Forest Laboratories, LLC v. Sigmapharm Laboratories, LLC, et al., Civil Action no 14-1110 (SLR)(SRF) (District of Delaware).

13. I am being compensated for my time spent in this matter at the rate of $850 per hour.

II. Assignment

14. I have been asked by counsel for Bard to provide a background primer describing how risk is assessed in epidemiology and the use of biostatistical methods in assessing risk.

15. I have also been asked to respond to arguments set forth in the Expert Report of Rebecca Betensky, PhD.

III. Summary of Opinions

16. I am prepared to provide at trial, with or without the assistance of visual aids, an explanation of the foregoing opinions, including the additional details of the opinions set forth below.

17. I may also provide a tutorial for the Court, if requested, on basic principles of interpreting epidemiological studies and biostatistics.

18. I base my opinions on my education, knowledge, my experience, and the documents and publications cited in my report below. A list of additional materials that I considered is attached as Exhibit 2.

IV. Background on Clinical Assessment of Risk and Biostatistical Methods

19. "Epidemiology is a field of public health and medicine that studies the incidence, distribution, and etiology of disease[1]," where "disease" is construed broadly to cover harmful health effects. This definition can include adverse events associated with medical devices. Epidemiologic evidence can identify treatments that are associated with increased risk of specific events. As such, epidemiologic studies can identify associations which may or may not be causal.

20. Pharmacoepidemiology, originally focused on the population effects of pharmaceutical agents, is the area of epidemiology that examines possible relationships between medical treatments (including the use of medical devices) and subsequent outcomes.

21. Pharmacovigilance denotes safety activities related to marketed drugs and devices. A key element of such activities are spontaneous adverse event reporting systems—such as MAUDE which is a device-related safety database maintained by the US Food and Drug Administration—to which occurrences of events that could possibly be related to specific treatments can be reported by health care professionals, manufacturers, and the general public. Such reporting systems are useful in identifying "signals" that may indicate a potential issue with a drug or device.

[1] Michael D. Green, D. Michael Freedman, and Leon Gordis. Reference guide on epidemiology. In *Reference Manual on Scientific Evidence*, pages 549–632. Federal Judicial Center, National Research Council of the National Academies, Third edition, 2011.

> While there have been many definitions of a signal put forth over the years, the important underlying principle is that a signal is a hypothesis that calls for further work to be performed to evaluate that hypothesis.[2]

A. Epidemiologic assessment of risk (including signal vs causation)

22. In the Summary of her January 2017 report, Dr. Betensky appears to addresses whether the risk of specific adverse events is greater for certain Bard filters than for the SNF filter, that is, whether the risk ratio exceeds one. For example, Dr. Betensky states that, "The Recovery filter is associated with statistically significantly *higher risks of the AE's* of interest than the SNF filter." (emphasis added)

23. However, as I discuss below, Dr. Betensky does not—and cannot—calculate those risks, much less the ratios of risks between Recovery filters and SNF filters, for instance. Therefore Dr. Betensky could not have made any direct assessment of statistical significance as it relates to the risk ratios comparing Bard removable filters to SNF filters. Instead, Dr. Betensky calculates a "reporting risk ratio" (RRR) for each adverse event, and she then performs statistical calculations that correspond to the RRRs.

24. The "reporting risk ratio" that Dr. Betensky reports is more accurately described as a "reporting rate ratio", as it reflects the rate at which particular events are reported to a database and has no direct relationship to the rate at which those events occur in patients.

[2] Gerald J. Dal Pan, Marie Lindquist, and Kate Gelperin. Postmarketing spontaneous pharmacovigilance reporting systems. In Brian L. Strom, Stephen E. Kimmel, and Sean Hennessy, editors, *Pharmacoepidemiology*, chapter 10, pages 137–157. John Wiley & Sons, Fifth edition, 2012, at 146.

25. Dr. Betensky states that "The reporting risk ratio is an estimate of the measure of interest, which is the risk ratio (RR)." Unfortunately, the RRR is a very poor estimate of the RR. As an estimate of the risk ratio, the RRR Dr. Betensky reports is subject to a range of biases, as she admits in her deposition, the possibilities of which Dr. Betensky either evaluates incompletely or not at all. Indeed, it is possible for the *risk of events* to be lower for one filter, while at the same time the *reporting rate* for that filter to be higher. In that case, the RRR would completely misrepresent the actual risk ratio.
26. Although Dr. Betensky is careful throughout the body of her report to emphasize that she is dealing with RRRs and not risk ratios themselves, that caution is omitted in her Summary conclusions.
27. Other experts have relied on Dr. Betensky's inaccurate and misleading summary of her work, to draw conclusions about the relative risks associated with one filter over another.
28. The essence of Dr. Betensky's argument in the Summary is that the RRRs she calculates are so large that the risk ratios (to which the RRRs are indirectly related) must also be large, or at least greater than one—in essence, because the RRRs smoke, the risk ratio, if only we could observe it, would reveal fire. For the reasons outlined below, such an argument is flawed.
29. To understand why the RRRs are extremely poor proxies for actual risk ratios, and why reporting risk ratios can exceed one even when the actual risk ratios are equal to or less than one, it is essential to understand what an appropriate risk ratio is, and how its components are related to the components of the RRR calculated by Dr. Betensky. Dr. Betensky never defines the risk ratio that her RRRs are intended to approximate. Had Dr.

Betensky done so, the tenuous relationship between the RRRs that she computes and the RRs would have become apparent.

30. For definiteness, let us consider a comparison of one filter (Filter 1) to another (Filter 2) with respect to the risk of a specified adverse event over a particular period of time. For example, we could compare the Recovery filter to the SNF filter through the third quarter of 2005 for caval perforation. One simple measure of risk for Filter 1 would be the fraction of Filter 1 patients in whom the event occurred, that is, the number of patients who actually experienced the adverse event during that time period (A_1) divided by the number patients who had Filter 1 implanted during that same period (N_1). This very simple measure of risk is thus

$\mathrm{Risk}_1^* = A_1/N_1.$

The risk for the SNF filter would be calculated in the analogous way. The risk ratio based on this measure is RR^*:

$\mathrm{RR}^* = \mathrm{Risk}_1^*/\mathrm{Risk}_2^*.$

31. There is a problem with these simple measures, however, and they generally aren't used because they omit a critical consideration. If patients' chances of experiencing an adverse event increase the longer their implants are in place, then patients whose implants are of longer duration are more likely to have an event than those whose filter was placed shortly before the end of the time period in question. In other words, a better measure of risk is the chance of having an event per year of exposure. If the average number of years of exposure of all patients implanted with Filter 1 is E_1, then the total amount of time to which all patients have been exposed is N_1 times E_1. Thus, a better measure of risk for Filter 1, expressed as risk per person-year of exposure is

$$\text{Risk}_1 = A_1/(N_1 \times E_1),$$

and the corresponding risk ratio is

$$\text{RR} = \text{Risk}_1/\text{Risk}_2.$$

32. In practice, neither A_1 nor N_1 nor E_1 can be directly observed. Instead, the risk measures and the risk ratio must be estimated based on data. The quality of the data used for this purpose depends upon the specifics of what is observed (measurement), how the data are collected (study design), and in whom the observations are made (patient populations). Each of these factors affects the quality of a particular estimate of the risk ratio.

B. Hierarchy of evidence: Experiment, prospective observation, retrospective observation, anecdote

33. Epidemiologists recognize a hierarchy of methodologies for estimating and comparing risks. From strongest evidence to the weakest, these general methods are: randomized clinical trials, prospective cohort studies, and controlled retrospective comparisons[3]. With the exception of clinical trials, epidemiologists must rely upon observational methods. Series of cases or collections of reports can provide limited information about possible risks. I will describe below how each such method would be applied in the context of comparing risks associated with two filter types, which I designate Filter 1 and Filter 2.

34. "The Achilles' heel of observational studies is the possibility of differences in the two populations being studied with regard to risk factors other than exposure to the agent.[4]"

[3] Two other methods lower on the evidentiary hierarchy, cross-sectional and ecological studies, are not discussed in this report. They present different issues and have different limitations from the methods discussed here.

[4] Green, Freedman, and Gordis, *supra,* at 556.

In the current setting, this refers to the possibility of differences between patients who received Filter 1 and those who received Filter 2 (the two populations of patients) with regard to factors that influence adverse events (risk factors) other than just having had Filter 1 or Filter 2 (the agents).

35. **Randomized clinical trials.** The strongest and most reliable evidence of risk, and the best evidence for comparing risk (say, through risk ratios) comes from randomized clinical trials. In these studies, each candidate for a filter would be randomly assigned to receive either Filter 1 or Filter 2. As a result, all factors that could affect the likelihood of an adverse event would be equally present, on average, in both groups of patients. Thus, any differences in adverse event rates between Filter 1 and Filter 2 in the study could not be due to differences in pre-existing risk factors. All patients in such a study would be monitored for occurrence of adverse events in the same way, so that differences in adverse event rates in the study could not be attributed to different likelihood of detecting an adverse event should it occur. The number of patients receiving each Filter type would be known, and the length of follow-up or exposure for each patient enrolled in the study would be monitored as well. Thus, in terms of the components of the risk calculation, we would have highly accurate estimates for each component of the risk calculation within the clinical trial: A_1, N_1, and E_1 for Filter 1, for instance. Moreover, the comparison of Filter 1 to Filter 2 is an apples-to-apples comparison: comparing similar patients treated similarly in every respect except for the assignment of implanted filter.

36. Clinical trials operate under a protocol that specifies how all study procedures will be carried out and how specific possible outcomes are defined. This is particularly important when the outcomes being assessed are adverse events. Having a common

definition of what counts as, for example, migration or tilt of a filter that applies in a uniform way and the does not rely on the subjective judgment of an investigator is an essential element.

37. For these reasons, randomized clinical trials provide a sound basis for estimating rates at which adverse events occur, and for comparing rates across products using rate ratios.

38. Because patients in a randomized clinical trial are assigned at random to Filter 1 and Filter 2, it is also possible to make sense of statistical assessments in such a context. For instance, if the observed relative risk is 4, indicating that the risk of the adverse event was observed to be four times greater for Filter 1 as for Filter 2, and if the results of a statistical assessment declares this observed RR to be "statistically significantly greater than 1," it means that the amount of excess risk observed for Filter 1 is greater than could plausibly be attributed to chance. That is, it is implausible to think that the higher risk seen with Filter 1 was purely a result of the chance allocation process and not to something that is different about treatment with the specific filters being studied. The statistical analysis compares the observed outcome of the study to what the random allocation method could have produced; thus, randomization is what provides a basis for statistical inference in a randomized trial.

39. **Prospective cohort studies.** In the absence of randomized trials, prospective cohort studies provide the next best level of evidence. In such studies, all patients in a defined population who receive either Filter are identified, and then closely monitored over time for occurrence of the adverse events of interest. Because we know who is in the study from the moment they are implanted, we know N_1 and N_2. Because the method by which the occurrence of adverse events will be monitored and ascertained, events that do occur

are just as likely to be detected regardless of which filter the patient received. Thus, ascertainment of A_1 and A_2 is comparable across treatments. And because patients in each group are followed in the same way, the amount of time that patients in each group are at risk (E_1 and E_2) is well-determined, too.

40. As with clinical trials, prospective cohort studies operate under a pre-specified study protocol that makes all study procedures uniformly applied across treatments and study centers.

41. While good evidence can be obtained from prospective cohort studies, they are prone to potential *biases* that typically do not arise in randomized clinical trials. In epidemiology and biostatistics, "bias" refers to a factor that is unrelated to the treatment effects under study that systematically influences the results in a certain direction.

42. Because filters are not randomly assigned in a prospective cohort study, it is important either to rule out or to control for differences in factors that affect both the likelihood of getting one filter over the other and the likelihood of an adverse event. Epidemiologists call one such potential issue of this sort "confounding by indication." For instance, if young active patients are preferentially given Filter 1, and if activity itself increases the risk of an event such as migration or tilting, then there would be a disproportionate number of such events seen in Filter 1 patients, whether or not the intrinsic risk of migration or tilt differed between Filter 1 and Filter 2.

43. If there were no difference in intrinsic risk between Filter 1 and Filter 2, the actual risk ratio would be equal to one (RR=1), but the *estimated* risk ratio from the study would be greater than one, leading to the erroneous conclusion that Filter 2 was safer than Filter 1. Epidemiologists have developed methods to account for biases of this type in prospective

cohort studies that arise from baseline differences. These methods include case matching, propensity-score matching, and regression methods.

44. Another key factor that contributes to the evidentiary strength of prospective cohort studies is uniformity of follow up across treatment groups. If, for instance, patients receiving Filter 1 were examined every three months to determine whether filter removal was appropriate, but if Filter 2 patients were only examined should a problem become manifest, then there would be more opportunities to detect asymptomatic adverse events for Filter 1 than for Filter 2, even if such events occurred at the same rate for both. This potential problem is obviated by a follow-up schedule and ascertainment protocol specified in advance, as is typically the case in prospective cohort studies.

45. For these reasons, prospective cohort studies can provide a sound basis for estimating rates at which adverse events occur, and for comparing rates across products using rate ratios, provided potential sources of bias are adequately accounted for.

46. Although the same statistical calculations used in randomized trials, perhaps after adjustment for identified confounders, can be carried out in prospective cohort studies, they always must be done with two large caveats. First, they are calculations "as if" assignments to treatment were the result of a randomization mechanism, even though the choice of treatment for each patient can be decidedly non-random. Second, those statistical calculations take no account of the extent to which there are unrecognized or unmeasured confounding factors that could introduce bias into the comparison.

47. I know of only one prospective cohort study examining the safety and efficacy of IVC filters. The PRESERVE study is a five-year study whose enrollment started in October of 2015[5]. Initial data collection for the PRESERVE study will be complete in 2018.

48. **Controlled retrospective studies**. Clinical trials and prospective cohort studies have the advantage that adverse events are ascertained in a systematic way over the course of the period starting with filter implant. Retrospective studies start with the identification of the adverse event, and then try to work backwards to assess the possible relationship of the events to possible factors that might increase their risk. The most commonly used study design of this type is the case-control study, in which (a) a number of individuals are identified who had the adverse event of interest (the "cases"), (b) a corresponding number of individuals with similar characteristics are identified who did not have the adverse event of interest (the "controls"), and then (c) differences in the frequency with which possible risk factors appear in the cases and controls are used to indicate possible causally related factors. It is essential in case-control studies that the cases and the controls be as similar as possible with respect to all known factors that are associated with the adverse event of interest. Case-control studies provide no basis for estimating risk, since the design provides no information about N1 (or E1). Consequently, case-control studies cannot produce estimates of risk rate ratios. Under certain limited circumstances, they can produce an estimate of a relative percentage risk, but not a rate ratio.

49. The interpretation of statistical tests in the context of case-control studies is subject to additional caveats beyond those intrinsic to prospective cohort studies; the conclusion

[5] [http://www.preservetrial.com; https://clinicaltrials.gov/ct2/show/study/NCT02381509]

that "differences are larger than could plausibly be attributed to chance" does not imply that such differences are due to differences in the treatments being compared, as they could easily result from risk factors that were not taken into account in matching cases and controls. Indeed, there is no identifiable chance mechanism at play in these studies.

50. **Case reports and case series.** Case series report the outcomes, typically from a single investigator, of consecutive patients treated using the same treatment. They can give some indication of risks that might occur in conjunction with that treatment, but they cannot provide a basis for quantitative assessment of risks in a general population, because there are no controls for such biases as patient selection and ascertainment bias.

51. Collections of case reports—essentially anecdotes—provide the lowest degree of information about possible risks, and provide no basis for quantitative estimation of risk. Such collections include no reliable basis for determining (or describing) the population of patients who were at risk of adverse events, no information about cumulative exposure, rely on no standardized method for defining and adjudicating events, are subject to confounding by indication, and can be affected by differential reporting.

C. Biostatistical methods and their application to risk assessment: significance tests and p-values, definition of "bias"

52. Dr. Betensky discusses two statistical procedures for comparing reporting rates for two filters: significance tests (and the *p*-values that summarize results from such tests) and confidence intervals.

53. A statistical test of significance assesses the extent to which an observed result calculated from a data set is consistent with a particular statistical scenario that could in principle have given rise to the data in the first place. The scenario to which the observed result is compared is called the "null hypothesis," from which a summary measure called the *p*-

value is calculated by assuming that a particular mathematical structure describe how the data arise. The American Statistical Association, in its Statement on Statistical Significance and *P*-Values[6] describes the interpretation of *p*-values succinctly: "The smaller the *p*-value, the greater the statistical incompatibility of the data with the null hypothesis, *if the underlying assumptions used to calculate the p-value hold.*" [emphasis added]. The ASA Statement continues by stating that "[s]cientific conclusions and business or policy decisions should not be based only on whether a *p*-value passes a specific threshold[7]" such as $p<0.05$.

54. While it is customary to describe comparisons that result in *p*-values less than 0.05 as being "statistically significant," it is important to note that "statistical significance" is a term of art that does not imply scientific, clinical, human, or economic importance. Even unimportant practical differences can give rise to very small *p*-values if the sample size on which it is based is sufficiently large, for instance[8].

55. Dr. Betensky provides an abbreviated description of her calculation as follows: "The p-value is the probability that the observed RRR (e.g., 4.4) or an even more extreme RRR (e.g., a larger value than 4.4 or a smaller value than 1/4.4) could have arisen if the true RRR is actually one. If the p-value is very small (e.g., less than 0.05), we either have to believe that a highly unlikely event occurred, or that our presumption that the true RRR is equal to one is incorrect."

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[6] Ronald L. Wasserstein and Nicole A. Lazar. The ASA's statement on p-values: Context, process, and purpose. *The American Statistician*, 70(2):129–133, Apr 2016, at 131.

[7] Wasserstein and Lazar, *supra* at 131.

[8] Wasserstein and Lazar, *supra* at 132.

56. Dr. Betensky's description omits important details. Specifically, Dr. Betensky neither mentions nor assesses whether the underlying assumptions used to calculate her p-values hold. As I describe in detail below, in all of the cases Dr. Betensky considers, those underlying assumptions simply do not hold.

57. In order to calculate any probability (including the probability calculation underlying the *p*-value), one must specify how chance or randomness enters into the data generating process. It makes no sense to ask whether a particular result could plausibly have arisen "by chance" if there is no understanding of how chance could have entered in the first place. There are two primary ways in which chance is assumed to enter in statistical calculations: either as the result of randomization (as in the case of a randomized clinical trial) or from random sampling a subset of a population.

58. Dr. Betensky also describes 95% confidence intervals, which she interprets as an interval in which we can be "95% confident" that the "true" reporting risk ratio lies. As with the term "significance", "confidence" as used here is a term of art. Dr. Betensky's description is inaccurate if we take the ordinary meaning of "confidence." Although a common misinterpretation, "the confidence interval does not give the probability that the unknown parameter lies within the confidence interval.[9]"

59. As with the *p*-value, however, that interpretation depends upon underlying assumptions about the data-generating mechanism. Those assumptions are identical to the ones on which *p*-values are based.

[9] David H. Kaye and David A. Freedman. Reference guide on statistics. In *Reference Manual on Scientific Evidence*, pages 211–302. Federal Judicial Center, National Research Council of the National Academies, Third edition, 2011, at 247.

D. Data sources and data quality

60. Dr. Betensky's analyses rely on two data sources: reports of adverse events drawn from the FDA's MAUDE data base, and tabulations of unit sales of specific filters by month (after 2002) provided by Bard. Both data sources have limitations.

61. MAUDE, the Manufacturer and User Facility Device Experience Database, is a database maintained by the US Food and Drug Administration that collects reports of adverse events associated with medical devices[10]. Reports can be made directly to the MAUDE system by physicians, healthcare professionals, hospitals, and patients. Reports from these sources are entirely voluntary.

62. In addition, device manufacturers are required to submit reports concerning all possible adverse events and device issues of which they become aware. Manufacturers become aware of possible reportable events through many channels, including information received from their representatives in the field, from distributors, from published literature, and from reports made directly to the manufacturer from patients, healthcare professionals, or other sources.

63. Because an event may be reported both directly to the MAUDE database and may also be reported to, or discovered by, the manufacturer separately, individual events may appear more than once in the MAUDE database.

64. Reports of potential adverse events are included in the MAUDE database whether or not they are confirmed.

[10] US Food & Drug Administration, Manufacturer and User Facility Device Experience Database – (MAUDE), https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/-PostmarketRequirements/ReportingAdverseEvents/ucm127891.htm, accessed 31 March 2017

65. The MAUDE database contains both adverse events *per se* and "product problems" that don't result in any adverse consequences to patients. As a result, not all reports contained in MAUDE are actual adverse events.

66. Because there is no requirement that healthcare professionals report adverse events to MAUDE, and because not all adverse events may be detected, MAUDE does not capture all cases of any event of interest. Consequently, it is not possible to calculate an incidence rate (or a risk rate) for a particular event with a particular device[11].

67. Because MAUDE reports generally contain no information about how long a device had been implanted prior to the reported event, it contains no information on the extent of patient exposure. Consequently, MAUDE can provide no information about the rate at which events may occur as a function of exposure time.

68. The FDA specifically cautions against using MAUDE data in several places: "MAUDE data is not intended to be used either to evaluate rates of adverse events or to compare adverse event occurrence rates across devices. "[12] The FDA also notes that "Although [medical device reports] are a valuable source of information, this passive surveillance system [MAUDE] has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use." [13] And,

[11] Dal Pan, Lindquist, and Gelperin, *supra* at 148.

[12] U. S. Food & Drug Administration, *supra.*

[13] U. S. Food & Drug Administration, MAUDE Database Search, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm, accessed 31 March 2017

"[medical device report] data alone cannot be used to establish rates of events, evaluate a change in event rates over time or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices."[14]

69. Spontaneous adverse event reporting systems such as MAUDE also do not contain information about the extent of utilization of any device. Since the number of events expected with a device grows with utilization, simply counting events (or even reports of events, which is what MAUDE contains) without accounting for differences in utilization is inappropriate.

70. Dr. Betensky uses data on sales in a given calendar period as a proxy for the number of implants made during that same period. Sales data, however, may have limited utility for this purpose. First, devices implanted during the period may have been sold to the hospital in a previous period. Second, devices that are sold may sit on the shelf (or may be returned, or damaged, or expire) and never be implanted. Third, the relationship of sales to implants can vary over the life span of a product. For instance, early on, sales may exceed implants as hospitals purchase initial stocks. Later, the rate at which devices are used may roughly equal replacement sales, and then when other products come into use, hospitals may deplete their inventories, in which case implants exceed sales.

71. A final aspect of data quality relates to the definitions used to define adverse events such as filter migration or filter tilt. Although Dr. Betensky refers to MAUDE reports as "adverse events", it is not clear that all such reports are actually of events that had an adverse impact on the patient in any way. Many of the reports on IVC filters in the

[14] *ibid*

MAUDE database report "product problems" and answer the question, "Is this an adverse event?" with "No." It is not clear whether definitions were used of what constituted an adverse event report for purposes of Dr. Betensky's analysis.

E. Relation of reporting-risk ratio (RRR) to risk ratio (RR)

72. Dr. Betensky calculates the "reporting risk" for a particular filter as the ratio x_1/n_1, where x_1 is the number of reported events in the MAUDE database during a specific period and n_1 is the number of units sold during that period. (I note that Dr. Betensky omitted the word "reported" when she describes the RRR, although it is clear that Dr. Betensky can only refer to *reported* AEs—and to a higher "risk" of reporting them, not of incurring them.)

73. It is instructive to compare Dr. Betensky's reporting rate—x_1/n_1—to the corresponding adverse event rate—$A_1/(N_1 \times E_1)$. Let's examine how $A_1$is related to x_1. Events that occur in a particular period are of three kinds: those that are not detected during that period, those that are detected and not reported in that period, and those that are both detected and reported during that period. Consequently, only events in the third category make it into MAUDE and are counted in x_1.

74. However, x_1 also contains events that occurred in earlier periods, since the MAUDE database records the date on which a report was received, not the date on which the possible adverse event occurred. Thus, it is not possible to match the time period in which an event occurred to the corresponding period in which the device was sold. As a result, the time periods covered by x_1 may not correspond to the time period covered by n_1 in Dr. Betensky's calculation.

75. When we turn to the denominator, we note two problems. First, as noted above, sales in a period have no direct relationship to the number of devices implanted during that same period, so that n_1 is an imperfect replacement for N_1. Second, Dr. Betensky's calculation does not involve any measure of the duration of use, E_1. The effect is the same as assuming that a patient's actual risk of experiencing an event is unaffected by the length of time that the patient's filter was implanted.

76. As a result of the factors identified above, the event reporting rate for a specific filter as used by Dr. Betensky (x_1/n_1) is subject to biases of unknown magnitude when used as an estimate for the actual adverse event rate ($A_1/(N_1 \times E_1)$).

77. To summarize, we can write the number of events reported (x_1) as the number of events that actually occurred (A_1) times the fraction of these events that were detected (d_1) times the fraction of detected events that were reported to MAUDE (r_1), that is,

$$x_1 = A_1 \times d_1 \times r_1,$$

where d_1 and r_1 reflect biases due to the detection and reporting of events associated with Filter 1.

78. Similarly, the number of devices implanted in a period (N_1) differs from the number of devices sold in that period (n_1) by the difference in the number of implanted units taken from inventory, that is previously sold, and the number of sold units placed into inventory, that is sold items not implanted. Depending on this difference, the number of sales can either overstate or understate the number of implanted devices, by a factor f_1 which reflects this bias. That is,

$$n_1 = N_1 \times f_1.$$

79. Because these biases can affect reporting for different filters in different ways, the "reporting risk ratio" on which Dr. Betensky relies can be even more seriously biased as an estimate of the actual event rate ratio.

80. Using a little bit of algebra, we can write the "reporting risk ratio" for a particular adverse event that Dr. Betensky relies on as an "estimate" for the risk ratio for that same event in the following way:

$$\mathrm{RRR} = \frac{x_1/n_1}{x_2/n_2} = \frac{A_1}{A_2} \times \frac{N_2}{N_1} \times \frac{d_1}{d_2} \times \frac{r_1}{r_2} \times \frac{f_2}{f_1},$$

which can also be written to show the relationship of Dr. Betensky's calculation to the risk ratio itself:

$$\mathrm{RRR} = \mathrm{RR} \times \frac{d_1}{d_2} \times \frac{r_1}{r_2} \times \frac{f_2}{f_1} \times \frac{E_1}{E_2}.$$

81. The four factors on the right are the amount by which the reporting risk ratio overstates the actual risk ratio.

V. Responses to Dr. Betensky's report

82. The data upon which Dr. Betensky relies do not support her conclusions. With respect to the hierarchy of evidentiary approaches that epidemiologists employ, I note that the data from the MAUDE data base on which Dr. Betensky relies are not data from a controlled study, whether prospective or retrospective. Instead, they are collections of spontaneously reported accounts of individual experiences—essentially collections of anecdotal reports. As such, they do not provide the benefits of bias control and validity that such features as randomization, prospective assessment, standardized assessment of outcomes, or controlled comparisons that other studies benefit from and that increase the reliability of their conclusions.

83. In the section of Dr. Betensky's report entitled "Potential Limitations and Responses", Dr. Betensky identifies underreporting of events as one possible bias. The factors d_1 and r_1 above determine the amount of underreporting for Filter 1, while d_2 and r_2 are the corresponding amounts for Filter 2. As Dr. Betensky notes, underreporting does not introduce bias into the estimation of RR, provided that the degree of underreporting is the same for the two filters. It is only differential underreporting that is important.

84. Dr. Betensky suggests that differential underreporting "does not seem plausible" for two reasons: First, Dr. Betensky states that since the calculated RRRs vary considerably from one adverse event type to the next, then "differential reporting would [also] have had to have been highly variable across adverse events." [page 11] This is incorrect. Variability in RRRs across events could be due to variability in the risk ratios. Moreover, to the extent that relative likelihood of detection (d_1/d_2) varies from one event type to another, and to the extent that some events when detected are more likely to be reported when associated with one filter than with another (r_1/r_2), variability in RRRs across adverse event types says nothing about the plausibility of differential underreporting.

85. Second, Dr. Betensky states that "given the magnitude of the RRR's, and their variability across adverse events, it seems implausible that differential underreporting by filter could fully explain the deviation of the observed RRR's from 1." [page 11] The key here is Dr. Betensky's use of the word "fully". It is entirely plausible that differential underreporting, together with the effects of differential biases in use of sales data (f_2/f_1) and failure to take differential length of exposure (E_1/E_2), could account for the deviation of the observed RRRs from one.

86. There are several reasons why there might there be a greater chance that an event would be detected for a removable filter compared to a permanent one. An event such as filter migration can be detected via imaging or during a surgical procedure (such as a filter retrieval procedure). If permanent filters are implanted and then ignored absent any problem, while removable filters are regularly monitored by imaging, then there would be more opportunities to detect events associated with the removable filters even if there is no greater risk for the event to occur. Dr. Betensky alludes to this possibility in her report ("especially if underreporting of SNF were due to decreased detection due to its permanence.") Similarly, if some events are discovered during a procedure to remove a temporary filter, only patients with such filters would have those otherwise undetected events found.

87. A second reason why there might be differential underdetection of events for removable and permanent filters is that if a substantial portion of the experience with permanent filters predates the introduction of removable filters, and if specific adverse events did not become recognized as potential problems until after the introduction of the latter, then detection of these events would fall disproportionately on removable filters.

88. A third reason why differential underdetection might be at play is that newly introduced treatments (i.e., drugs and devices) receive greater scrutiny (and receive more reported adverse experiences) than established treatments. In general, the efforts to monitor devices are likely to be greater when they are new than when they have been long established, and increased monitoring leads to increased detection of events that have actually occurred. To the extent that the time periods studied include early years of use

for removable filters and not for permanent filters, differential detection would be likely to occur.

89. Fourth, if the standard of care as it relates to monitoring that could detect effects requires greater or more frequent follow up for filters intended to be removed than for those intended to be permanent, the increased surveillance would lead to differential detection.

90. Fifth, if the standard of care as it relates to monitoring affected all implanted filters equally, but the fraction of filters that were removable increased over the course of the time period at issue, the average detection rates would be higher for removable than for permanent filters.

91. All of the potential biases related to differential underdetection (d_1/d_2) would work to cause the RRR to be an overstatement of the actual risk ratio.

92. There are also reasons why, when events are actually detected, recoverable filters might have differential reporting rates compared to permanent filters (r_1/r_2). In her section on Limitations, Dr. Betensky discusses the possibility that reporting could be effected by publicity or notoriety, a well-known effect[15]. Dr. Betensky dismisses this possibility by noting that an FDA warning letter sent to Bard post-dates the data on which her calculations are based, and therefore that letter could not have affected the figures that she calculates. However Dr. Betensky neglects to consider other possible types of stimulated reporting that may have differentially affected retrievable and permanent filters.

93. One such source of stimulated reporting occurs when individuals who have had an event with a retrievable filter are systematically identified with a view toward submitting

[15] Dal Pan, Lindquist, and Gelperin, *supra,* at 151.

reports to the filters' manufacturer, while no corresponding effort is made to identify individuals who may have had an event with a permanent filter. Any such reports received by the manufacturer are required to be submitted to the FDA and would be represented in the MAUDE database.

94. In such cases, it is possible that the reports made as a result of event solicitation can duplicate reports already made through physicians, patients, and other sources, thus being double-counted in the MAUDE database. As Dal Pan, Lindquist, and Gelperin note, "this issue is a potential source of bias and limits the utility of data mining and other calculations which rely on 'crude' case counts that have not been 'de-duplicated'."[16] Dr. Betensky does not address this issue.

95. I note, for instance, that in the period between December 1, 2009 and July 31, 2010, the period that separates Dr. Betensky's last two sets of calculations, the number of reports for filter migration more than doubled for the Recovery filter compared to the entire past history of reports for migration, increasing from 38 reports in the period through the end of November, 2009 to a total of 78 by the end of July, 2010. This is despite the fact that the Recovery filter had not been on the market for over four years by that time. *See* Exhibit 3.

96. A similar phenomenon can be observed for the G2 retrievable filter. The G2 filter was introduced in August 2005. By mid-2006, there had been about 1.31 reports of migration for every thousand G2 filters sold. Over the next 17 months, there were 0.83 such reports for every thousand G2 filters sold. Over the 24-month period after that, the number of reports had declined to 0.43 per thousand. Then, starting in the 7-month period

[16] Dal Pan, Lindquist, and Gelperin, *supra,* at 151.

beginning December 1, 2009, the rate went up to 9.43 reports per thousand G2 filters sold, a 22-fold increase. [These are based on the figures reported in Dr. Betensky's spreadsheets.]

97. I did a search of the MAUDE database for the period December 1, 2009 through July 31, 2010 searching for all events reported concerning the G2 filter; 122 such reports were identified, with links to each report starting with the most recent. Of the first ten returns from the database, four were reported to the manufacturer on the same day (July 9, 2010). The event descriptions of all four events were identical[17]. In each case, the Reporter Occupation was listed as "Attorney." This suggests to me that stimulated reporting that differentially affects retrievable as opposed to permanent filters is at least plausible.

98. As Dr. Betensky notes, increased reporting can also be observed soon after the launch of a drug (or device) and then decrease over time (the "Weber effect"). Dr. Betensky argues that such an effect is unlikely at play here because the RRRs are increasing over time rather than decreasing. A look at the data above for the G2 filter shows precisely what the Weber effect would predict: an initial high reporting rate: a higher rate than subsequently seen in the first year of introduction, followed by reduced reporting rates over the next three-plus years. The same pattern is seen for caval perforation as for migration in these data (except caval perforation saw almost a 70-fold spike in reports in the 7-month period from December 2009 through July 2010).

[17] "Event Description: It was reported that allegedly the ivc filter fractured, and the fractured portions of the device migrated to the patient's vital organs causing injury and damage. No specific information is available at this time."

99. Consequently, the data are consistent with both a Weber effect and separate stimulated reporting, both of which would act to increase reported events for retrievable filters but not for permanent ones. Dr. Betensky did not evaluate these possibilities in her report.

100. The next component in the relation between the RRR calculated by Dr. Betensky and the actual risk ratio is the difference in the effects on denominators of the reporting rates, that is, the differences between sales and implants. Dr. Betensky purports to address this issue by "discounting the sales numbers by 20%". Doing so has no effect whatsoever on the calculated RRRs, because it *assumes* that the factors by which sales and implants differ operate identically for retrievable as for permanent filters. As Dr. Betensky notes, "[i]f the proportion of filters implanted among those sold does not differ by filter, then this overestimation of exposure does not affect the risk ratio estimation." But Dr. Betensky makes no effort to determine whether those proportions do in fact differ by filter.

101. The final component that relates the RRR to the actual risk ratio is the ratio of average exposure time, that is, the average time that implants are in place for each implanted patient (E_1/E_2). Dr. Betensky notes that "estimates are not comparable among products that have different overall person time at risk, unless the risk of the AE is highest close to its implantation and declines after that." Dr. Betensky then dismisses this concern by stating that "it is reasonable to assume that adjusting for calendar years of sales, there would be greater person time at risk associated with SNF than with Recovery." Dr. Betensky provides no reason to think that this is reasonable at all. For instance, if the average remaining life expectancy of patients implanted with the SNF filter was very short, while retrievable filters were implanted in patients who were

generally healthier and more likely to have greater residual life expectancies, then many (or most) of the SNF patients considered in Dr. Betensky's report would no longer be at risk, while many (or most) of the retrievable-filter patients would be.

102. A factor related to differences in life expectancy is the potential for confounding, which occurs when specific patient characteristics "are associated both with use of a particular device, such as Recovery, and with the AE, such as migration. If the analysis is conducted without adjustment for confounders, the RRR may be biased for the RR." [Betensky at page 13] Although Dr. Betensky states that she is not aware "of any individual level data that include potential confounding factors," confounding factors can introduce bias whether or not there is data available that could be used to adjust for confounding if present. If, for example, retrievable filters are preferentially used over permanent filters in younger, more active patients (i.e., age and activity are associated with choice of device) and if more active patients are more likely to dislodge an implant resulting in migration (association with the AE), then confounding is present and would bias the RRR upward, even if the RR is actually one. I note that the ACR Practice Parameter regarding intra-vena caval filters states that "[t]he use of retrievable filters should also be considered in pediatric and young adult patients."[18]

103. Dr. Betensky's discussion of Limitations to her analysis also discusses counting and data errors, in which Dr. Betensky notes that "even small errors can have large effects on small numbers of events" such as those related to SNF event reports in the RRRs that she calculates. Dr. Betensky conducted a sensitivity analysis by adding 5 to

[18] American College of Radiology. *ACR-SIR practice parameter for the performance of inferior vena cava (IVC) filter placement for the prevention of pulmonary embolism*. American College of Radiology, 2014.

the reported counts for each category of adverse event for the SNF filter, in effect, allowing x_2 to be 5 events larger. This has a large effect on the RRRs. For instance, the RRR for migration for the G2 filter compared to the SNF filter drops from 144 to 24—only one sixth as great. In other words, even small errors in the counts of reported events can have large effects on the quantity that Dr. Betensky relies on to estimate the risk ratio.

104. I disagree with Dr. Betensky's statement in the Summary that "if the estimated risk ratios had been condidered to be due to an imbalance in the reporting of adverse events, given their large magnitudes, it seems that the company likely would have carefully evaluated this through increased monitoring. This does not appear to have been done." In my experience, device manufacturers have no ability to identify patients who have been implanted with their devices, much less to monitor them. Physicians monitor patients and their outcomes, not device manufacturers. In any event, Dr. Betensky provides no basis for her conclusion about what the company did or did not do.

105. In her summary Dr Betensky argues that, while there are several potential issues with the data, no one of them by itself can account for the large RRRs if in fact there is no elevation in risk for retrievable filters over permanent ones. By looking at each such issue in isolation, Dr. Betensky ignores the likelihood that many of these issues operate simultaneously. When taken in concert, the numerous potential biases and data issues can easily produce large RRRs even if there is no actual elevation in risk among comparable patients.

106. Dr. Betensky cites the "consistency over time" in her results as support for conclusions related to increased risk of adverse events. This consistency, however, is a

consequence of the fact that Dr. Betensky relies on cumulative sales and adverse event report counts. Thus, for instance, almost 95% of the sales on which Dr. Betensky's July 2010 calculations are based are included in the November 2009 data. It is not surprising that the results bear similarity to one another. The consistency of results is a consequence of how the data were examined. Consequently, they do not lend added weight to Dr. Betensky's claim that reporting rate ratios can be used as proxies for event rate ratios.

VI. Conclusions

107. Dr. Betensky employs adverse event reports from the MAUDE data base for a purpose for which they were not intended and against which the FDA explicitly warns.

108. The "reporting risk ratios" that Dr. Betensky reports do not directly estimate risk ratios for adverse events between retrievable and permanent filters.

109. The "reporting risk ratios" that Dr. Betensky reports are subject to important and potentially substantial biases, each of which has the potential to substantially over-estimate the true risk ratio.

110. Dr. Betensky either ignores or does not adequately investigate the extent to which these potential biases could be applicable to the case at hand. In each case, there are biases that are plausibly at play that were neither investigated nor ruled out.

111. The statistical calculations that Dr. Betensky reports can apply at best only to comparisons of reporting rates and not to comparisons of adverse event rates. Moreover, because there is no element of either randomization or random sampling, there is no basis for statistical inference based on those calculations.

112. The statements in the Summary of Dr. Betensky's report that claim "statistically significantly higher risks of the AE's" of interest relative to the SNF filter are incorrect.

Dr. Betensky carried out no statistical analysis of "risks of AEs" (as opposed to the chances that AEs would be reported). Moreover, Dr. Betensky calculated no direct estimates of the relative rates at which adverse events occur.

113. I disagree with Dr. Betensky's statement that the "extremely large magnitudes of the reporting risk ratios suggest that … the risk ratios for the adverse events could still be considerably larger than 1." [page 14] As shown in my analysis above, the reporting risk ratios could plausibly be inflated by factors between 20 and 70 for differential reporting alone. When combined with possible effects of differential detection, differential estimation of number of implants, differential exposure, and confounding factors, obtaining "extremely large" reporting risk ratios could be achieved even if the true risk ratio were one or less.

114. For the reasons discussed in detail above, my conclusion is the opposite of Dr. Betensky's. Specifically, the available adverse event data on which Dr. Betensky relies provides no compelling evidence in favor of increased risks of adverse events.

I hold each of the opinions in this report to a reasonable degree of scientific certainty.

SUPPLEMENTATION

I hereby reserve any rights that I may have to supplement this report.

Ronald A. Thisted, Ph.D.

13 April 2017

Date

Exhibit 1

Ronald A. Thisted

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B.A. (Mathematics, Philosophy) Pomona College, 1972. Magna cum laude

Professional:

All at the University of Chicago:

2014– Vice-Provost, Academic Affairs
2009– Member, Committee on Clinical and Translational Science
2007–2014 Director, Population Sciences, Institute for Translational Medicine
2005– Member, Center for Cognitive and Social Neuroscience
2001–2008 Member, Institute for Mind and Biology
2000–2014 Director, Biostatistics Core Facility, University of Chicago Cancer Research Center
1999–2012 Chairman, Department of Health Studies (now Public Health Sciences)
1999–2012 Co-Director, Clinical Research Training Program
1996– Professor, Department of Public Health Sciences (Health Studies until 2014)
1993–1998 Co-Director, Robert Wood Johnson Clinical Scholars Program
1993– Professor, Committee on Clinical Pharmacology and Pharmacogenomics
1992– Professor, Departments of Statistics, Anesthesia & Critical Care, and the College
1989–1992 Associate Professor, Department of Anesthesia and Critical Care
1982–1992 Associate Professor, Department of Statistics and the College
1979–1982 Leonard Jimmie Savage Assistant Professor, Department of Statistics and the College
1976–1982 Assistant Professor, Department of Statistics and the College

Honors:

Phi Beta Kappa, Pomona College, 1972.
Sigma Xi, The University of Chicago, 1977.
The Llewellyn John and Harriet Manchester Quantrell Award for Excellence in Undergraduate Teaching, 1981.

Professional Societies:

American Association for the Advancement of Science (Elected Fellow, 1992)
1994–1997 Electorate Nominating Committee, Section on Statistics
American Statistical Association (Elected Fellow, 1988)
1987–1989 Section on Statistical Graphics, Chair (1988)
1994–1996 Executive Committee, Section on Statistical Education
1994–1996 Section Representative, Section on Statistical Computing
Association for Computing Machinery
International Biometric Society, ENAR
Institute of Mathematical Statistics
1987–1990 Nominating Committee
1989–1993, 1999–2002 Management Committee, *Current Index to Statistics*
Royal Statistical Society
Society for Industrial and Applied Mathematics, (Visiting Lecturer, 1979–80)

Editorial:

Computing Reviews, Reviewer (1978–1987).
J American Statistical Assoc, Associate Editor (1979–1985, 1987–1988).
SIAM J Scientific and Statistical Computing, Editorial Board (1983–1985).
ACM Trans on Math Software, Associate Editor (1990–1992).
Current Index to Statistics, Database Ed. (1994); Managing Ed. (1995); Editor (1996–1998).

Selected Publications

Books

[1] *Elements of Statistical Computing: Numerical Computation.* Chapman & Hall: London. 1988.

[2] The Chicago Social Brain Network. *Invisible Forces and Powerful Beliefs: Gravity, Gods, and Minds.* FT Press Science: Upper Saddle River, NJ. 2010.

Original Articles

[2] "The Prediction of Homicide with the Rorschach" (D Lester, J Kendra, R Thisted, W Perdue). *J. Clinical Psych.,* **31**, (1976), 752.

[3] "Estimating the Number of Unseen Species: How Many Words Did Shakespeare Know?" (B Efron, RA Thisted). *Biometrika,* **63**, (1976), 435-447.

[4] *Ridge Regression, Minimax Estimation, and Empirical Bayes Methods.* Ph.D. Thesis, Department of Statistics, Stanford University (1976).

[5] "Prediction of Homicide and Suicide: A Test in a Healthy Risk-Taking Group" (D Lester, JM Kendra, RA Thisted). *Perceptual and Motor Skills,* **44**, (1977), 222.

[6] "Teaching Statistical Computing Using Computer Packages" (with Discussion), *The American Statistician,* **33**, (1979), 27–35.

[7] "User Documentation and Control Language I: Evaluation and Comparison of Statistical Computer Packages." *Computers & Education,* **3**, (1979), 135–141.

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[10] "Maximum Likelihood Estimation of Isotonic Modal Regression" (T Sager, R Thisted). *Annals of Statistics,* **10**, (1982), 690–707.

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[16] "Did Shakespeare Write a Newly-Discovered Poem?" (R Thisted, B Efron). *Biometrika,* **74**, (1987), 445–455.

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Jaureguito, JF Wilcox, SJ Cohn, RA Thisted, B Reider). *American Journal of Sports Medicine,* **23,** (1995), 350–3.

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Computer Software and Data Bases

[S1] *The Literary Detective* (SA Kurtz, RA Thisted). Version 0.14. Computer software for Macintosh computers. The University of Chicago: Chicago, Illinois. 1989.

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Book Chapters, Comments, Reviews, and Other Publications

[M1] Comment on "A Simulation Study of Alternatives to Ordinary Least Squares," by Dempster, Schatzoff, and Wermuth, *Journal of the American Statistical Association,* **72**, (1977), 77–106.

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[M3] *Statistical Methods for Digital Computers*, by Enslein, Ralston, and Wilf. (Book review) *Computing Reviews,* **20**, (1979), 309–312.

[M4] Comment on "A Critique of Some Ridge Regression Methods," by Smith and Campbell, *Journal of the American Statistical Association,* **75**, (1980), 81–86.

[M5] "The Effect of Personal Computers on Statistical Practice". *Computer Science and Statistics: Thirteenth Symposium on the Interface*, W. F. Eddy, ed. (1981), 25–30.

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[M12] "The Use of Computers in Statistical Research," (WF Eddy, PJ Huber, DE McClure, DS Moore, W Stuetzle, R Thisted). Report of an Institute of Mathematical Statistics Panel. (1986). Reprinted as Eddy, WF. "Computers in Statistical Research," *Statistical Science,* **1(4)**, 1986, 419–437.

[M13] "Knowledge Representation For Expert Data Analysis Systems," in *Computer Science and Statistics: 17th Symposium on the Interface,* DM Allen, ed. North-Holland (1986), 43–48.

[M14] "Representing Statistical Knowledge and Search Strategies for Expert Data Analysis Systems," Chapter 11 in *Artificial Intelligence and Statistics,* William A. Gale, editor. (1986) Addison-Wesley: Reading, Massachusetts. 267–284.

[M15] "Tools for Data Analysis Management," in *Computer Science and Statistics: Eighteenth Symposium on the Interface,* Thomas Boardman, Editor. (1986) American Statistical Association: Washington, 152–159.

[M16] "Sources of Error in Graphical Perception: A Critique and an Experiment" (M Morris, R Thisted). *Proceedings of the Section on Statistical Graphics.* (1986). American Statistical Association: Washington, 43–48.

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[M18] Comment on "Collinearity and least squares regression," by G. W. Stewart, *Statistical Science* **2**, (1987), 91–93.

[M19] *Statistical Image Processing and Graphics*, Edward J. Wegman and Douglas J. DePriest, editors. (Book review) *Technometrics* **30**, (1988), 126–127.

[M20] *Graphical Exploratory Data Analysis*, by S. H. C. du Toit, A. G. W. Steyn, and R. H. Stumpf. (Book review) *Journal of the American Statistical Association,* **84**, (1989), 614.

[M21] "Distribution of Editorial-Board Membership for Statistics Journals," (Letter) *The American Statistician,* **45**, (1991), 170–171.

[M22] *Linear Least Squares Computations,* by R. W. Farebrother. (Book review) *Technometrics,* **33**, (1991), 368–369.

[M23] "Complications of Patients Undergoing Lumbar Discectomy in Community Hospitals," (L Ramirez, R Thisted). chapter in *Complications of Spinal Surgery,* Edward Tarlov, ed., American Association of Neurological Surgeons: Park Ridge, (1991).

[M24] "Computers and Modern Statistics," (RA Thisted, PF Velleman). Chapter 3 in *Perspectives on Contemporary Statistics,* David Hoaglin and David F. Moore, eds. Mathematical Association of America: Washington. (1992).

[M25] "Interdisciplinary Statistics Education." In *Modern Interdisciplinary University Statistics Education: Proceedings of a Symposium,* Committee on Applied and Theoretical Statistics, National Research Council (1994), 110–116.

[M26] *Artificial Intelligence Frontiers in Statistics,* D. J. Hand, editor. (Book review) *Journal of the American Statistical Association,* **89**, (1994), 719–720.

[M27] "Incidence of postdural puncture headache in morbidly obese parturients [letter]," (E Faure, R Moreno, R Thisted). *Regional Anesthesia,* **19(5)**, (1994), 361–363.

[M28] "On 'Smoking is not a predictor of mortality and morbidity following coronary artery bypass grafting' by JR Utley, et al." (Invited Commentary) (J Olak, R Thisted) *Journal of Cardiac Surgery,* **11,** (1996) 385–6.

[M29] "Re: Long-term survival and mortality in prostate cancer treated with noncurative intent [letter; comment]," (GW Chodak, RA Thisted), *Journal of Urology,* **155**(6), (1996), 2039; discussion 2039–41.

[M30] Comment on "The Gaussian Hare and the Laplacian Tortoise: Computability of Squared-Error versus Absolute-Error Estimators," by Stephen Portnoy and Roger Koenker, *Statistical Science,* **12**, (1997), 296–298.

[M31] "6-Mercaptopurine and Mesalamine for prevention of relapse after conservative surgery for Crohn's Disease," [Reply to Letter] (SB Hanauer, R Cohen, RA Thisted, P Rutgeerts, DH Present, BI Korelitz), *Gastroenterology*, **128**(1), (2005), 249–251.

[M32] "Treatment of Crohn's disease: the 'Long' of it," [Editorial] (SB Hanauer, RA Thisted), *Gastroenterology*, **128**(7), (2005), 2164–6.

[M33] "Baseline Adjustment: Issues for Mixed-Effect Regression Models in Clinical Trials," *ASA Proceedings of the Joint Statistical Meetings,* 386–391. American Statistical Association (Alexandria, VA). (2006).

[M34] "Happiness and the invisible threads of social connection: The Chicago Health, Aging, and Social Relations Study." (JT Cacioppo, LC Hawkley, A Kalil, ME Hughes, L Waite, RA Thisted). Chapter 10 in *The Science of Subjective Well-Being,* Michael Eid and Randy J. Larsen, eds. Guilford Press: New York. (2008), 195–219.

[M35] "Multilevel investigations: Conceptual mappings and perspectives." (JT Cacioppo, GG Berntson, RA Thisted). Chapter 17 in *Biosocial Surveys,* Committee on Advances in Collecting and Utilizing Biological Indicators and Genetic Information in Social Science Surveys. M Wienstein, JW Vaupel, and KW Wachter, eds. The National Academy Press: Washington, DC (2008), 367–380.

[M36] "Epilogue." Chapter 16 in *Invisible Forces and Powerful Beliefs: Gravity, Gods, and Minds,* The Chicago Social Brain Network. FT Press Science: Upper Saddle River, NJ. (2010) 197–205.

Selected Grants and Contracts
Completed and Ongoing

R01 HD069500 Lauderdale, D (PI) 7/1/2011–8/31/2014 (NIH/NIA)
Social Relationships, Economic Shocks, Sleep and Wellbeing Among Older Adults
Role: Co-Investigator, Biostatistician

P30 CA14599 Le Beau, M. (PI) 05/1/08–03/31/18 (NIH/NCI)
UCCRC-Cancer Center Support Grant; Subproject: Biostatistics Facility
Role: Scientific Director of Biostatistics

UL1 TR000430 Solway, J. (PI) 9/17/07–05/31/17 (NIH)
Clinical and Translational Science Award
Roles: Population Sciences Cluster Director, Clinical Research Training Program Co-Director

U01 DK62429 Cho, J (PI) 9/30/02–11/30/17 (NIH/NIDDK)
IBD Genetics Consortium Data Coordinating Center
Role: Director, Data Management Core (Site PI)

HHSA 290-2007-10058 Meltzer, D (PI) 10/26/09–10/25/12 (AHRQ/ARRA/BCBS)
American Recovery and Reinvestment Act of 2009: Comprehensive EPC Comparative Effectiveness Reviews for Effective Health Care
Role: Statistical consultant

R34 AI080962 Solway, J (PI) 9/4/08–8/31/09 (NIH/NIAID)
Evaluation of Lovastatin in Severe Persistent Asthma (ELiSPA)
Role: Co-Investigator, Biostatistician

5K30 HL04093-02 Coe, F. (PI) 6/1/99–9/27/07 (NIH)
Clinical Research Training Program
Roles: Program Co-Director, Seminar Director

P01 AG18911 Cacioppo, J. (PI) 7/1/01–6/30/06 (NIH)
Social Isolation, Health and the Aging Process; Biostatistical Core B
Role: Director, Biostatistics Core

R01 CA92443-01 Meltzer, D. (PI) 9/1/01–8/31/04 (NIH)
Cost-Effectiveness of Prostate Cancer Screen/Treatment
Role: Advisory Panel

R01 HS09982 Thisted, R. (PI) 9/15/99–8/31/03 (AHRQ)
Patient Preferences for Disclosure: A National Survey
Role: Principal Investigator (*vice* Levinson), Statistician

R01 NS40229 Frank (PI) 9/18/99–6/30/03 (NIH)
Hemicraniectomy for Swelling from Cerebral Infarction
Role: Director, Data Coordinating Center

Cassell, C. (PI) 7/1/93–6/30/95
Thisted, R. (PI) 7/1/95–6/30/98
Levinson, W. (PI) 7/1/98–6/30/01
Lantos, J. (PI) 7/1/02–6/30/06 (Robert Wood Johnson Foundation)
Clinical Scholars Program
Role: Co-PI to 1998, Co-Director to 1999; Core-Faculty; Advisory Board

Teaching

Recent Courses Taught

2014 Health Studies 310: Epidemiologic Methods
Health Studies 333: Longitudinal Data Analysis
Health Studies 307: Clinical Epidemiology (Lecture: Meta-Analysis)
Essentials of Patient-Oriented Research (Lecture: Study Design)

2013 Health Studies 307: Clinical Epidemiology (Lecture: Experimental Study Design)
Essentials of Patient-Oriented Research (Lecture: Study Design)
Health Studies 333: Longitudinal Data Analysis

2012 Health Studies 307: Clinical Epidemiology
Health Studies 333: Longitudinal Data Analysis
Seminar in Clinical Research Methods (20 weeks)
Medicine 777: Advanced Clinical Pharmacology (Lecture: Pharmacoepidemiology)

2011 Health Studies 329: Introduction to Clinical Trials
Health Studies 333: Longitudinal Data Analysis
Seminar in Clinical Research Methods (30 weeks)
Medicine 777: Advanced Clinical Pharmacology (Lecture: Pharmacoepidemiology)

2010 Health Studies 327: Biostatistical Methods
Health Studies 333: Longitudinal Data Analysis
Seminar in Clinical Research Methods (30 weeks)
Medicine 777: Advanced Clinical Pharmacology (Lecture: Pharmacoepidemiology)

2009 Health Studies 327: Biostatistical Methods
Seminar in Clinical Research Methods (30 weeks)
Medicine 777: Advanced Clinical Pharmacology (Lecture: Pharmacoepidemiology)
Family Medicine 304: Epidemiology and Clinical Investigation (Lecture: Screening Tests)

2008 Health Studies 327: Biostatistical Methods
Seminar in Clinical Research Methods (30 weeks)
Statistics 307/Computer Science 378: Numerical Computation

2007 Health Studies 327: Biostatistical Methods
Seminar in Clinical Research Methods (30 weeks)
Medicine 777: Advanced Clinical Pharmacology (Lecture: Pharmacoepidemiology)
Statistics 307/Computer Science 378: Numerical Computation

2006 Health Studies 327: Biostatistical Methods
Seminar in Clinical Research Methods (30 weeks)
Medicine 777: Advanced Clinical Pharmacology (Lecture: Pharmacoepidemiology)

2005 Statistics 307: Numerical Computation
Seminar in Clinical Research Methods (30 weeks)

2004 Health Studies 327: Biostatistical Methods
Health Studies 541: Epidemiology and Clinical Investigation
(Lecture: Chronic Disease Epidemiology)
Medicine 777: Advanced Clinical Pharmacology (Lecture: Pharmacoepidemiology)
Medicine 603: Critical Appraisal of Medical Literature (Lecture: Statistical issues)
Seminar in Clinical Research Methods (30 weeks)

2003 Health Studies 541: Epidemiology and Clinical Investigation
Health Studies 327: Biostatistical Methods
Medicine 777: Advanced Clinical Pharmacology (Lecture on Pharmacoepidemiology)

Medicine 603: Critical Appraisal of Medical Literature (Lecture: Statistical issues)
Seminar in Clinical Research Methods (30 weeks)

2002 Health Studies 541: Epidemiology and Clinical Investigation
Medicine 777: Advanced Clinical Pharmacology (Lecture on Pharmacoepidemiology)
Medicine 603: Critical Appraisal of Medical Literature (Lecture: Statistical issues)
Seminar in Clinical Research Methods (30 weeks)

2001 Health Studies 541: Epidemiology and Clinical Investigation
Statistics 224: Applied Regression Analysis
Medicine 777: Advanced Clinical Pharmacology (Lecture on Pharmacoepidemiology)
Medicine 603: Critical Appraisal of Medical Literature (Lecture: Statistical issues)
Seminar in Clinical Research Methods (30 weeks)

2000 Health Studies 541: Epidemiology and Clinical Investigation
Statistics 224: Applied Regression Analysis
Medicine 777: Advanced Clinical Pharmacology (Lecture on Pharmacoepidemiology)
Seminar in Clinical Research Methods (30 weeks)

1999 Statistics 307: Numerical Computation
Statistics 226: Categorical Data Analysis
Seminar in Clinical Research Methods (15 weeks)

Refereeing, 2005–

Annals of Statistics
Regulatory Pharmacology and Toxicology
Journal of Clinical Oncology
Journal of Surgical Research
Neuropsychopharmacology
Perspectives in Biology and Medicine
PLoS ONE
Statistics in Medicine
NIH, Center for Scientific Review (Surgery, Anesthesiology and Trauma study section)
NIH, Center for Scientific Review (Challenge Grant Editorial Panel HDM-P)
NSF, Division of Mathematical Sciences
Research Grants Council of Hong Kong

University Committees

Current appointments:

Innovation, Transparency, Conflict of Interest, 2015–.
Compliance Committee, 2014–.
Committee on Academic Fraud, 2014–.
Committee on Individual Conflict of Interest 2015–.
Executive Committee, Center for Cognitive and Social Neuroscience, 2007–.

Previous appointments (since 1989):

ad hoc Committee for the Spring 2015 Climate Survey on Sexual Misconduct, 2015.
Executive Committee, Institute of Translational Medicine (CTSA), 2007–2015.
Steering Committee, Spring 2016 Climate Survey on Diversity and Inclusion, 2015–2016.
Committee on Appointments and Promotions, Biological Sciences Division, 2014.
Data Stewardship Committee, University of Chicago Medicine, 2013–2014.
Health Professions Faculty Advisory Committee, 2013–2014.
Center for Research Informatics Oversight Committee, 2011–2014.
Research Advisory Committee, University of Chicago Medicine, 2010–2014.
Research Planning Review Committee, University of Chicago Medicine, 2012–2013.
Committee of Basic Science Chairs, Biological Sciences Division, 1999–2012.
Executive Committee, Clinical Research Training Program, 1999–2012.
University of Chicago Medical Center, Budget Oversight Committee, 2007–2010.
Executive Committee, Division of Biological Sciences, 2000–2009.
ad hoc Faculty Science Review Committee, 2009.
Committee of Clinical Chairs, Biological Sciences Division, 1999–2006.
Executive Committee, University of Chicago Cancer Research Center, 2000–2005.
Advisory Committee, Robert Wood Johnson Clinical Scholars Program, 1999–2006.
Search Committee (Chair), Chairman of Department of Psychiatry, 2003–2004.
Committee to Review Appointments and Promotions, 2003–2004.
Tenure and Tracks Committee, 2003–2004.
Committee to Advise the Provost on Federal Wide Assurance (Chair), 2003.
Research Aims Committee, Division of Biological Sciences, 2002–2003.
Search Committee, Chairman of Department of Obstetrics & Gynecology, 2000–2003.
Committee to Advise the President on the Dean of the Biological Sciences Division, 2001–2002.
Search Committee, Chairman of Department of Family Medicine, 2000–2002.
Provost's Committee on Medical Informatics, 2000–2001.
Clinical Translational Advisory Group, Biological Sciences Division, 1999–2001.
Co-chair, Committee on Law and Medicine, BSD and Law School, 1999–2000.
Working Group on Clinical Data Sharing, 1999–2001.
Executive Committee, Department of Anesthesia & Critical Care, 1994–1998.
Institutional Review Board, Division of Biological Sciences, 1983–1986, 1987–1997.
Faculty Campus Planning Committee, 1993–1996.
College Curriculum Committee, 1990–1996.
Board of Computing Activities and Services 1981–1986, 1991–1994.
Physical Sciences Division, Space/Facilities Committee, 1992–1994.
Committee on Family Practice (BSD), 1993.
Provost's Committee on Health Studies, 1993.
Health Studies Committee (BSD), 1991–1992.
College Council, 1979–1982, 1983-1986, 1989–1992.

Exhibit 2

References

American College of Radiology. *ACR-SIR practice parameter for the performance of inferior vena cava (IVC) filter placement for the prevention of pulmonary embolism*. American College of Radiology, 2014.

Gerald J. Dal Pan, Marie Lindquist, and Kate Gelperin. Postmarketing spontaneous pharmacovigilance reporting systems. In Brian L. Strom, Stephen E. Kimmel, and Sean Hennessy, editors, *Pharmacoepidemiology*, chapter 10, pages 137–157. John Wiley & Sons, Fifth edition, 2012.

Michael D. Green, D. Michael Freedman, and Leon Gordis. Reference guide on epidemiology. In *Reference Manual on Scientific Evidence*, pages 549–632. Federal Judicial Center, National Research Council of the National Academies, Third edition, 2011.

David H. Kaye and David A. Freedman. Reference guide on statistics. In *Reference Manual on Scientific Evidence*, pages 211–302. Federal Judicial Center, National Research Council of the National Academies, Third edition, 2011.

Predicting the Safety and Effectiveness of Inferior Vena Cava Filters (PRESERVE). ClinicalTrials.gov registry. Last updated March 23, 2017. https://clinicaltrials.gov/ct2/show/study/NCT02381509 Accessed 12 April 2017

The PRESERVE trial. http://www.preservetrial.com Accessed 12 April 2017.

Reference Manual on Scientific Evidence, Third edition. Federal Judicial Center, National Research Council of the National Academies, 2011.

Brian L. Strom, Stephen E. Kimmel, and Sean Hennessy, editors. *Pharmacoepidemiology*, Fifth Edition. John Wiley & Sons: New York, 2012.

US Food & Drug Administration, Manufacturer and User Facility Device Experience Database – (MAUDE), https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/-PostmarketRequirements/ReportingAdverseEvents/ucm127891.htm, accessed 31 March 2017.

U. S. Food & Drug Administration, MAUDE Database Search, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm, search terms: Device="Filter, Intravascular, Cardiovascular"; Brand Name="G2"; Report Date From="12/1/2009"; Report Date To="7/31/2010". Page Last Updated: 02/28/2017. Accessed 31 March 2017.

Ronald L. Wasserstein and Nicole A. Lazar. The ASA's statement on p-values: Context, process, and purpose. *The American Statistician,* 70(2):129–133, Apr 2016.

Exhibit 3

G2 filter reporting rates, by time period

Cumulative (from Betensky)

	n	migr	perf	migr/1000	perf/1000
q3-05	1447	0	0	0.00	0.00
Jun-06	16783	22	20	1.31	1.19
Nov-07	61182	59	24	0.96	0.39
Nov-09	115136	82	38	0.71	0.33
Jul 10	122031	147	161	1.20	1.32

By period

n	migr	perf	migr/1000	perf/1000
15336	22	20	1.43	1.30
44399	37	4	0.83	0.09
53954	23	14	0.43	0.26
6895	65	123	9.43	17.84
	last 7 month increase		22.11	68.75

Exhibit 4

Ronald Thisted, M.D.
INTERNAL LIST OF MATERIALS RECEIVED

ARTICLES

TITLE	AUTHOR(S)
ACR-SIR-SPR Practice Parameter on Informed Consent for Image-Guided Procedures (2016)	
Prevalence and clinical consequences of fracture and fragment migration of the Bard G2 filter: Imaging and Clinical Followup in 684 Implantations	An
Comparison of Complication Rates Associated with Permanent and Retrievable Inferior Vena Cava Filters: A Review of the MAUDE Database	Andreoli
Technical success and safety of retrieval of the G2 filter in a prospective, multicenter study	Binkert CA
Eight-Year Follow-Up of Patients with Permanent Vena Cava Filters in the Prevention of Pulmonary Embolism	Decousus
Evidence-Based Evaluation of Inferior Vena Cava Filter Complications Based on Filter Type	Deso
G2 Inferior Vena Cava Filter - Retrievability and Safety	Hearns
Fracture and Distant Migration of the Bard Recovery Filter: A Retrospective Review of 363 Implantations for Potentially Life-Threatening Complications	Tam

OTHER MATERIALS

2016.07.26 - Austin, Clare - Deposition of Rebecca Betensky Full Transcript
2016.07.26 - Austin, Clare - Deposition of Rebecca Betensky Condensed Transcript
Expert Report -- Bates -- 2017-02-10 (Barraza)
Expert Report -- Eisenberg -- 2017-02-10 (Barazza)
Expert Report -- Garcia and Streiff -- 2017-03-03 (MDL)
Expert Report -- Hertz -- 2017-02-02 (Barazza)
Expert Report -- Kessler -- 2016-09-27 (MDL)
Expert Report -- Kessler -- 2017-03-03 (MDL)
Expert Report -- Kinney, Roberts, Kalva -- 03-06-2017 (MDL)
Expert Report -- Betensky -- 2017-02-10 (Barazza)
Expert Report -- Betensky -- 2017-03-03 (MDL) Exhibit C to Report
Expert Report -- Betensky -- 2017-03-03 (MDL)
Expert Report -- McMeeking -- 2017-03-03 (MDL)
Expert Report -- Parisian -- 2017-03-03 (MDL)
Expert Report -- Ritchie -- 2017-03-02 (MDL)
Expert Report -- Vogelzang -- 2017-03-03 (MDL)
Betensky Report and Chart
Betensky Data for Service
2017.02.10 Barraza, Maria et al. - Expert Report of Rebecca Betensky, Ph.D

EXHIBIT I

Rebuttal Report to Dr. Feigal's Expert Report

Summary: This report responds to portions of the Report of Dr. Feigal dated March 17, 2017. I may or may not agree with opinions of Dr. Feigal and other defense experts upon which I have not commented. The main points of my rebuttal are the following:

- The FDA website suggests that MAUDE data can be used in conjunction with other data sources to provide information on adverse events. I agree with this, and accordingly identified the caveats and limitations of this analysis in my expert report.
- BARD has made repeated use of IMS sales data for other manufacturers' devices in their own statistical analyses, and so they apparently did not discount this approach.
- Dr. Feigal refers to the risk ratio and risk or incidence rate interchangeably. This is not correct, as they are different measures.

1. In Section IV.C.3.D of his report, Dr. Feigal selectively quotes from the FDA webpage on medical device reports and states: As FDA points out, "The MAUDE data is not intended to be used either to evaluate rates of adverse events or to compare adverse event occurrence rates across devices."

   Response: This statement is found at the following web address: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/ucm127891.htm. At the web address referenced by Dr. Feigal, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Search.cfm, which he actually quotes in Section V of his report, the following, similar, but more nuanced statement, is provided by the FDA:

   - "MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
   - Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
   - MAUDE data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions."

   Importantly, this FDA statement acknowledges that while MDR data should not be used in isolation, it does not advise against the type of analysis that I used in this case. There is nothing in any FDA statement that I have seen that precludes use of adverse event data in conjunction with other information to establish rates or events, to evaluate changes in

event rates over time, to compare event rates between devices, and to make device-related decisions.

The FDA published a guidance document on this topic, "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment," in 2005 (https://www.fda.gov/downloads/RegulartoryInformation/Guidances/UCM126834.pdf). The document clearly states that analyses of the FDA databases can provide insights into adverse events for a given product, and into comparisons between products. The following are selected quotations from the guidance document:

"Data mining can be used to augment existing signal detection strategies and is especially useful for assessing patterns, time trends, and events associated with drug-drug interactions."

"Although all of these approaches are inherently exploratory or hypothesis generating, they may provide insights into the patterns of adverse events reported for a given product relative to other products in the same class or to all other products."

"Although we recognize these limitations, we recommend that sponsors calculate crude adverse event reporting rates as a valuable step in the investigation and assessment of adverse events. FDA suggests that sponsors calculate reporting rates by using the total number of spontaneously reported cases in the United States in the numerator and estimates of national patient exposure to product in the denominator."

"Comparisons of reporting rates and their temporal trends can be valuable, particularly across similar products or across different product classes prescribed for the same indication. However, such comparisons are subject to substantial limitations in interpretation because of the inherent uncertainties in the numerator and denominator used. As a result, FDA suggests that a comparison of two or more reporting rates be viewed with extreme caution and generally considered exploratory or hypothesis-generating."

2. In Section V of his report, Dr. Feigal states: "While comparative reporting ratios, not risk, can be calculated from spontaneous report databases and FDA and others have developed methodology to examine reporting behavior [40,77, 117, 118] None of the sources previously cited by plaintiffs experts use these methods. Although Bard calculated the ratio of report over sales, as discussed above, the lack of direct information about sales of products other than their own makes comparisons between products meaningless. One important conclusion of the reporting rate statistical methods is that comparisons between various products do not establish differential risk only differential reporting. Risk must be evaluated by methods other than spontaneous reports."

Response: While Dr. Feigal states here that Bard's comparisons of reports over sales for their products to reports over sales for other manufacturers' products is meaningless due to the lack of direct information about sales of other manufacturers' products, Bard did not agree with this. As Dr. Feigal notes in Section III of his report, Bard used the IMS sales data for other products to make these comparisons: "Examination of individual reports is the best use of spontaneous reports, as they may identify previously unrecognized problems, and, of course, manufacturers have a responsibility to follow-up with individuals who report problems, which Bard did. They also tracked the number of reports against Bard sales to detect reporting trends. They collected MAUDE reports of non-Bard filters and examined comparative reporting rates based on estimates of sales from IMS [153], again to look at reporting trends."

There are multiple examples of Bard's use of adverse event data in a manner consistent with my use of that data, and contrary to the opinions of Dr. Feigal. In particular, in many different analyses, Bard used IMS sales data in comparisons between Bard products and those of other manufacturers (e.g., BPVE-01-00511127; BPVE-01-0101982; BPV-17-01-00153578).

In addition, although direct sales information about competitor products may be more accurate than IMS (which provides estimated sales information), the estimates and information derived from them are not "meaningless." Rather, there are potential limitations that can be considered when interpreting the results of analyses based on IMS data.

3. As quoted above from Section V of his report, Dr. Feigal claims that "One important conclusion of the reporting rate statistical methods is that comparisons between various products do not establish differential risk only differential reporting."

Response: This is not correct. As I point out in my expert report (Limitations and responses, underreporting), the reporting risk ratio can be expressed as $(a_1/a_2)\times RR$, where a_1 is the percentage of occurrences of the adverse event that are reported for device 1 and a_2 is the percentage of occurrences of the adverse event that are reported for devise 2 and RR is the risk ratio in the absence of any underreporting (or overreporting). This expression elucidates that

a. The reporting risk ratio combines the differential reporting ratio (a_1/a_2) with the risk ratio, RR. Thus, Dr. Feigal's claim that the reporting risk ratio only can establish differential reporting is incorrect.
b. If there is not differential reporting for the two devices, i.e., a_1 a_2, then the reporting risk ratio is a valid estimate of the true risk ratio.

In general, as I point out in the extensive Potential limitations and responses section of my report, there are several potential limitations to MAUDE data and estimates based on

them must be interpreted in light of these potential limitations. This interpretative stance is required for many human studies, even for randomized, double blind clinical trials, which lose their simplicity once participants are noncompliant or drop-out. Certainly it is required for non-randomized prospective studies, for cross-sectional studies, and for retrospective studies.

4. Dr. Feigal claims at the end of the same paragraph from Section V of his report (see item 2 above) that "Risk must be evaluated by methods other than spontaneous reports."

   Response: This statement deviates from the implication of statements of the FDA at their MAUDE homepage, as quoted by Dr. Feigal (and quoted above) that spontaneous reports can be used in conjunction with other information. In particular, the FDA states that the MDR data should not be used "alone" or "in isolation," suggesting that it could be used in conjunction with other data. Indeed, there are two studies published in peer reviewed journals (Angel, *et al.*, and Andreoli, *et al.*) in which the investigators analyzed MAUDE data to estimate complication rates concerning IVC filters. In the Andreoli, study, [1] the investigators "…compare[d] the safety of permanent and retrievable inferior vena cava (IVC) filters by reviewing the …(MAUDE) database."[2] The researchers concluded that the "MAUDE database reveals that complications occur with significantly higher frequency with [retrievable IVC filters] compared with [permanent IVC filters]."[3] Bard's G2 and G2X filters were included in the analysis. And in a review of data from clinical trials and the MAUDE database, Angel, *et al.* (2011) found, "All filters were associated with an incidence of significant migration of <1% with the exception of the G2 filter (Bard Peripheral Vascular, Tempe, Arizona), for which the incidence of significant migration was 4.5%." They also reported "most of the migration events (127 of 500 [25%]) in the MAUDE database were associated with the G2 filter (Table 5)," and "[m]ost of the fracture reports in the MAUDE database were associated with the G2 filter (157 of 500 [31%]) (Table 5).[4] I also am aware of studies of other medical devices that used and analyzed MAUDE data. [5] There are other examples.

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[1] Andreoli, et al., Comparison of Complication Rates Associated with Permanent and Retrievable Inferior Vena Cava Filters: A Review of the MAUDE Database, *J Vasc Interv Radiol* 2014; 25:1181-85 at 1181.

[2] *Id.* (abstract)

[3] *Id.*

[4] Angel LF, Tapson V, Galgon RE, Restrepo MI, Kaufman J. Systematic review of the use of retrievable inferior vena cava filters. J Vasc Interv Radiol 2011;22(11):1522–1530.e3

[5] Harth, et al, Major Complications Associated With Xenograft Biologic Mesh Implantation in Abdominal Wall Reconstruction, SURG INNOV December 2009 vol. 16 no. 4 324-329.

5. In Section V of his report, Dr. Feigal discusses at length the reasons why the MDR reports are an unreliable source to construct rates. He concludes this discussion by stating that MDR reports "is not a valid source to calculate rates and proportions of filter complications."

   Response: This concluding remark is Dr. Feigal's first mention of calculation of proportions. A proportion is not a rate, but is simply the number of events divided by the number of sales. In my report, I use the term "risk" to mean proportion, and I distinguish this from a rate, which I agree cannot be calculated (see my section on Potential limitations and responses, No person-time exposure/cannot calculate incidence rates and ratios). In fact, as I explain throughout my report, risks (i.e., proportions), and risk ratios can be calculated from the MAUDE data.

6. Dr. Feigal continues in Section V to state that "the numerator of these reports, the MDR reports, are an unreliable source to construct rates…"

   Response: For the numerators, i.e., the adverse event counts, I used Bard's own data. I assumed that Bard deemed these as sufficiently reliable to undertake the type of analyses noted above, and I note that this is an accepted method of analysis, which is used by manufacturers (including Bard) to evaluate their products and is published in peer-reviewed literature. While it is true that an individual report may contain inaccuracies, one must consider biases that are differential between products to establish that the conclusions drawn are invalid, as discussed in my earlier reports. As with all data, there are limitations in the use of MDR adverse event data, which must be considered in interpreting the results of analyses using the data.

7. In his paragraph beginning "I also disagree with opinions in Dr. Parisian's report" in Section V of his report, Dr. Feigal again confuses the notions of risk and incidence rate. He disagrees with Dr. Parisian that it is possible to determine comparative risk of complications from MAUDE reports. He then claims that Dr. Parisian also agreed with this in her deposition (in contradiction with her report), when she stated that "FDA says that you can't use incidence rates from the MAUDE database."

; William, et. al, Failure Rate Analysis of Femoral Stems from the MAUDE Database. Poster No. 2049 • *55th Annual Meeting of the Orthopaedic Research Society (published online at* ***http://www.ors.org/Transactions/55/2049.pdf*** ***;*** Dibardino, et al, Analysis of the US Food and Drug Administration Manufacturer and User Facility Device Experience database for adverse events involving Amplatzer septal occluder devices and comparison with the Society of Thoracic Surgery congenital cardiac surgery database, J Thorac Cardiovasc Surg 2009;137:1334-41

Response: Dr. Feigal fails to recognize that Dr. Parisian's report and deposition statements are not in contradiction at all, as Dr. Parisian makes statements about risk in her report, while she was asked about the incidence rate at her deposition.

8. Dr. Feigal states that my "assertion that the MDR reports are comparable across time ignores the potential differences in types of patients that received permanent and retrievable filters, and the potential differences in the detection of adverse events in those patient populations."

   Response: In the Potential limitations and responses/No person-time exposure/cannot calculate incidence rates and ratios section of my report I explicitly address the issue of permanence versus retrievability in the filters. In particular, I note that the reporting risk ratio of any Bard product relative to SNF that I present is likely an underestimate of the reporting incidence rate ratio. This is because the SNF was a permanent device, while the other products were retrievable, which translates into larger average exposure to SNF than to other products. Because the reporting incidence rate ratio is the average exposure time to SNF divided by the average exposure time to a different product multiplied by the reporting risk ratio, the reporting incidence rate ratio is very likely larger than the reporting risk ratio.

9. Dr. Feigal further states that I also ignore "the changes in medical practice that could increase the detection of the potentially asymptomatic filter adverse events over time."

   Response: Any symptomatic adverse event would not be affected by changes in medical practice. Regarding asymptomatic adverse events, changes in medical practice are also unlikely to explain the reporting rate differences demonstrated because the differences were apparent immediately after the launch of the Recovery and were consistent over time, suggesting a device issue rather than a change in medical practice. Moreover, an increase in medical device reports overall is unlikely to have any effect unless it is differential between retrievable and permanent devices. The fact that the FDA has noted an overall increase in medical device adverse event reports does not explain the effect seen in my analysis. Similarly, I have not seen evidence that stimulated reporting or reporting by lawyers regarding IVC filters could explain the results. Finally, Dr. Feigal's point is speculative and not supported by data that he has presented.

10. Dr. Feigal remarks that I make "the kinds of comparisons, across devices, that FDA points out cannot be done from MDR reports."

    Response: As I have noted in items 1 and 4 above, this is a misstatement of the FDA position as put forth on their MAUDE web page. The implied FDA position is that use of

the MAUDE database to compare devices and to estimate adverse event proportions can be done, but must be interpreted in light of other evidence and cannot stand alone or in isolation.

11. Dr. Feigal remarks that I do not use statistical methods for signal detection, which serve as a tool to identify "previously unrecognized signals of potential associations between a drug and an adverse event." He states that my characterization of my results as risk ratios is not correct.

    Response: Dr. Feigal is correct that I do not use these methods for signal detection. This is because the analysis that I undertook was hypothesis driven and was not exploratory. The hypothesis that I was asked to test was whether the reporting risk for SNF was the same as that for each of several Bard devices with respect to a well-defined, small set of pre-identified adverse events. The methods to which Dr. Feigal refers are intended for general monitoring of adverse events. They are exploratory and examine many different adverse events. The statistical underpinnings of the methods correct for the massive multiple testing that occurs as a result of this monitoring for any signal of adverse event.

12. Dr. Feigal states that my characterization of my results as risk ratios is not correct.

    Response: A careful reading of my expert report will reveal that I consistently characterize my results as reporting risk ratios and not as risk ratios. Where I use "risk ratios" in my report is in reference to the true (sometimes referred to as the actual) risk ratio and not any estimates based on MAUDE data.

13. Dr. Feigal states that I provided little discussion of how the assumptions of my statistical methodology were met.

    Response: The statistical tests and associated confidence intervals and p-values that I calculated assume statistical independence across adverse events among the population at risk for them. While this assumption may not be completely true, any substantial dependence across adverse events is likely to be local (i.e., within small clusters that would be defined by shared physicians or practices, for example), which would likely have a negligible effect on the inference. In the presence of weak positive correlation, the p-values may be very slightly under-estimated. Given the large and heterogeneous population from which the events are drawn, moderate or strong correlation would be very unlikely and thus a large under-estimation of the p-values is very unlikely. Regarding the concern that the events may not be identically distributed, in the context of this analysis, in which individual level factors are unknown and unavailable, the results are valid and applicable at the population level.

14. Dr. Feigal states that there is no evidence that my methodology "included any evaluation of the individual cases for case selection nor that she had a protocol to construct the populations used in her report."

Response: I included all cases that were included in the Bard internal documents in their adverse event counts and their sales data. I explained in my report every time I found a data error or discrepancy and how I handled it. These could not have been part of a protocol that was established prior to the analysis, as these specific situations could not have been anticipated prior to reviewing the data sheets. The "Data inconsistencies and errors" section of my expert report thoroughly details these cases.

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Rebecca Betensky, Ph.D.

April 20, 2017
Date